

PCTWORLD INTELLECTUAL PROPE
International Bi

INTERNATIONAL APPLICATION PUBLISHED UNDER

WO 9608289A1

(51) International Patent Classification ⁶ : A61M 37/04, 5/30		A1	(11) International Publication Number: WO 96/08289
			(43) International Publication Date: 21 March 1996 (21.03.96)
(21) International Application Number: PCT/IB95/00841		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).	
(22) International Filing Date: 12 September 1995 (12.09.95)		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(30) Priority Data: 08/304,274 12 September 1994 (12.09.94) US			
(60) Parent Application or Grant (63) Related by Continuation US 08/304,274 (CON) Filed on 12 September 1994 (12.09.94)			
(71) Applicant (for all designated States except US): SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES, S.A. [FR/FR]; 51-53, rue du Docteur-Blanche, F-75016 Paris (FR).			
(72) Inventor; and (75) Inventor/Applicant (for US only): CHERIF-CHEIKH, Roland [FR/FR]; 30, avenue Bourgain, F-92130 Issy-les-Moulineaux (FR).			
(74) Agents: VOSSIUS, Volker et al.; Holbeinstrasse 5, D-81679 München (DE).			
(54) Title: NEEDLE-LESS PARENTERAL INTRODUCTION DEVICE			
(57) Abstract			
<p>A needle-less device for the parenteral administration of a medicament is disclosed. The medicament has the shape of one end of a toothpick. It is palced in the bore of a barrel with the barrel having the shape of a nose cone at one end. A plunger is inserted into the other end of the bore. The plunger forces the medicament through the skin and into the subcutaneous layer of the patient without the need for penetration of the skin by a needle.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

- 1 -

NEEDLE-LESS PARENTERAL INTRODUCTION DEVICEField of the Invention

The present invention relates to parenteral
5 introduction devices and, in particular, to a device for
intramuscular or subcutaneous administration of a
pharmaceutically active composition.

Background of the Invention

The parenteral route is preferred over oral ones
10 in many occurrences. For example, when the drug to be
administered would partially or totally degrade in the
gastrointestinal tract, parenteral administration is
preferred. Similarly, where there is need for rapid
response in emergency cases, parenteral administration is
15 usually preferred over oral.

Thus, while parenteral administration is desirable
in many applications, as it is currently practiced, it
presents substantial drawbacks. Probably the biggest
drawback is the discomfort which it causes the patient to
20 whom the drug is being administered. Parenteral
preparations generally contain a large volume of liquid
in which the drug is suspended or dissolved. Ratios of
active ingredient to carrier commonly run from 1:100 to
1:1000. Especially where the active ingredient is poorly
25 soluble or difficult to suspend, or when it has to be
administered at high doses, or in both instances, a
fairly large volume of liquid must be injected. The
injection of the needle and the introduction of a fairly
large volume of liquid cause parenteral administration to
30 be more or less painful, and at least disagreeable, for
most people. Furthermore, depending on its nature, the

- 2 -

solvent or the suspending agent may itself be a cause of pain.

A further disadvantage to administration of drugs in a liquid carrier is that the drugs are frequently not stable in the liquid. Therefore, the liquid and drug must be mixed substantially contemporaneously with injection. This can be of substantial disadvantage where, for example, many hundreds of people must be treated over a course of days in order to stem an epidemic.

Accordingly, it would be interesting to find a mode of administration avoiding the use both of a needle and of a liquid solution or suspension.

Parenterally administered solid compositions for use in the controlled release of a medicament are known and devices allowing direct injection of a medicament without need of a liquid are known such as, for example, trocars for implants of rods or pellets, and the device shown in European Patent Application No. 0292936 A3 for injection of a solid. However, trocars and the device of European Patent Application No. 0292936 A3 still require use of a needle.

Summary of the Invention

The applicant has now discovered a comparatively inexpensive device for the ready administration of solid or semi-solid drugs by the parenteral route. The applicant's device avoids completely the need for a needle. The solid drug is injected directly through the skin of a patient, e.g., a human or animal, by a plunger which enters the skin only to the degree necessary to position the solid drug. The medicament is suitably made in the shape of the end of a toothpick, i.e., it has a pointed end which gradually tapers to a cylindrical portion. The medicament has sufficient structural

- 3 -

strength so that it can penetrate through the skin into the subcutaneous layer when it is administered with the parenteral introduction device of the present invention. Thus, the drug penetrates the skin and there is no need
5 for the expense of discomfort of a needle to administer the drug parenterally. The present invention also includes an automatic device that can contain a number of doses of medicament which can be administered to a series of patients, one after the other.

10 Other features and advantages of the invention will be apparent from the drawings, detailed description, and from the claims.

Brief Description of the Drawings

Fig. 1 is an exploded view of the parenteral
15 introduction device according to the present invention;

Fig. 2 shows the parenteral introduction device of the present invention in its retracted form;

Fig. 3 shows the device of the present invention with a medicament having been parenterally introduced
20 into a patient;

Fig. 4 shows the device of the invention with an automatic system where the plunger is replaced by a means for delivering pressurized gas; and

Fig. 5 shows an alternative embodiment of the
25 automatic device for administering seriatim shots to a number of individuals.

Detailed Description

Referring first to Fig. 1, which is an exploded view of the parenteral introduction device of the present
30 invention, there are three essential elements, namely a main barrel 10, a sleeve member 12, and a plunger member 14. The main barrel 10 has central bore 16 which extends from one end 22 to the other end 20 of the main barrel

- 4 -

10. A medicament 18 (see Fig. 2) is carried in this central bore 16. The main barrel 10 includes protruding ring members 24 and 26 which act as stops as will be hereinafter discussed. The sleeve member 12 is open at
5 both its top 28 and bottom 30 ends. The sleeve member 12 includes shoulders 32 and 34 to limit travel of the sleeve as hereinafter discussed. Plunger member 14 includes a plunger rod 36 and an end cap 38. The end cap 38 has a circular plate member 40 and a toroidally shaped
10 flange 42. The plunger rod 36 has an external diameter at least a portion of which is substantially the same as, or slightly smaller than, the internal diameter of the bore 16.

Fig. 2 shows the parenteral introduction device of
15 Fig. 1 in assembled condition and in a condition suitable for transport and storage. Plunger member 14 is press fit onto the end 28 of sleeve 12. Sleeve 12 has been forced over main barrel 10 so that shoulder 32 has passed over ring member 24 and has come to rest against ring
20 member 26. The sleeve member is in sliding engagement with the exterior surface of the main barrel 10. Abutment of shoulder 32 with ring member 26 restrains the relative position of the sleeve 12 and the main barrel 10 so that the plunger 14 does not inadvertently dislodge
25 the medicament 18 and push it through the said one end 22 of the main barrel 10. Ring member 24 prevents the unintentional separation of sleeve 12 from main barrel 10 since it will engage shoulder 32 before the sleeve 12 and the main barrel 10 are separated.

30 A seal 44 of biologically compatible material, such as cellulose or gelatin, may be applied to the end 22 of the main barrel 10 in order to maintain the sterility of the medicament 18 until the time it is administered. Alternatively, or additionally, the entire

- 5 -

mechanism can be stored in a sterile environment such as a foil or cellophane pack (not shown).

Turning now to Fig. 3, there is shown the device in use. The said one end 22 of the main barrel 10 has
5 been placed against the skin 48 of the patient to be treated, in such a way as to apply a tension on the zone where the medicament is to be injected. The plunger 14 and the sleeve 12, which travel together, have been urged down the main barrel 10 by applying pressure on the end
10 cap 38 of plunger 14 until shoulder 34 comes into contact with the ring member 24. The plunger rod 36 has traversed the length of the bore 16 of the main barrel 10 and has pushed the medicament 18 through the skin 48 of the patient and into the subcutaneous layer 46. Shoulder
15 34 of sleeve 12 in combination with ring member 24 of main barrel 10 has limited the extent of travel of the plunger rod 36 in the main barrel 10. It is preferred that the rod 36 of plunger member 14 stop no more than 2 mm below the said one end 22 of the main barrel 10 and it
20 is most preferred that the plunger member not extend at all beyond the said one end 22 of the main barrel 10.

In Fig. 4, there is shown an alternative embodiment of the present invention. In the alternative embodiment, the plunger 14 is replaced by a means for
25 providing gas pressure from a reservoir 52 and through a valve 54. The medicament 18 travels through barrel 56 under pressure of the gas. Barrel 56 can be replaced for each new injection. When an injection is to be made, button 58 is depressed. This allows pressure to flow
30 from reservoir 52 through valve 54 and regulator 60. The gas then forces the medicament 18 through the barrel 56 and into the patient (not shown). In the automatic device, this force is always the same because the amount of pressure exerted on the medicament is controlled by

- 6 -

the regulator 60. Thus, the force of the injection is independent of any force applied by the operator.

In Fig. 5, there is disclosed an alternative embodiment of the automatic injector of Fig. 4. In this alternate embodiment, means are provided for injection of a plurality of doses to successive individuals using only a single injection device. This embodiment is illustrated in Fig. 5 where there is a magazine 62 which has a plurality of bores 64 with a medicament 18 fitted into each bore 64. As in the device of Fig. 4, gas pressure forces one of the medicaments 18 into a patient when button 58 is depressed. After delivery of the first medicament, the magazine 62 is moved to the left so that the next adjacent bore 64 and its associated medicament 18 are positioned above the barrel 56. The button 58 can be depressed to create a new gas pressure and to inject this next medicament 18 into the next patient, and thereafter, the rest of the medicaments 18 can similarly be administered seriatim to a series of individuals. Movement of the magazine can be effected manually or can be done automatically in a known manner.

All of the components of the device may suitably be made of plastic material, but it is preferred that the automatic device be made of metal, notably stainless steel. For the manual device, the plunger 36 can be made of metal, but it can also be made of plastic if its cross-section is increased sufficiently. Even where the plunger 36 is made of steel, it may be less expensive to make than the usual syringe since the device of the present invention does not require a stainless steel needle, the making of which requires quite a bit of precision. The main barrel 10 is preferably made with a nose cone shape at end 22. The main barrel can be made as a single piece, or, alternatively, the space between the outside wall 50 of the main barrel and wall of the

- 7 -

central bore 16 can be hollow. The sleeve 12 is preferably made of transparent material so that the plunger rod 36 can be viewed therethrough, thus providing visual assurance that it is in its operative position.

5 The medicament 18 is preferably made of the shape of one end of a toothpick so that it can easily penetrate the skin and enter the subcutaneous layer. As is well known, one end of a toothpick has a point which tapers back to a cylindrical portion. The medicament is
10 referred to as solid; however, it may be either solid or semi-solid so long as it has sufficient structural integrity to penetrate the skin without breaking apart. It has been found that a medicament having a crush strength of at least about 8 killipoise in the
15 longitudinal direction is sufficiently strong, and lesser crush strengths are also usable, especially for administration to children, who have more tender skin than adults.

 The amount of carrier in the medicament 18 depends
20 on the drug and on the desired mode of action. As a general rule, the amount of active ingredient in the medicament is at least about 50%. With suitable medicaments which will have sufficient structural strength, the amount of medicament in the present
25 invention can be up to 100%. The medicament may be prepared by conventional techniques such as compression, thermofusion, or extrusion. Compression suitably consists of a tableting process in which a toothpick-shaped microtablet is formed. Thermofusion suitably
30 consists of mixing and melting of the active ingredients and a carrier, if desired. The melted product is then molded into the toothpick-shaped medicament. Extrusion suitably consists of mixing the active ingredients and carrier, if desired, with a liquid to form a semisolid
35 paste. The paste is then forced through a small diameter

- 8 -

opening to form a rod. The needle-like tip can be formed prior to or after drying of the semisolid rods.

The size of the medicament 18 may be up to 2 mm in diameter but is preferably from about 0.2 to 0.8 mm, and most preferably from about 0.25 to 0.5 mm, in diameter for the cylindrical portion of the medicament, and about 1 mm to about 3 cm in length. The size will depend, of course, on the dose to be administered and the level of active ingredient present as compared to the amount of carrier.

The inside diameter of the bore 16 is preferably about 5-10% larger than the diameter of the medicament 18. This helps to ensure that the medicament does not get "hung up" or striated by minor imperfections, such as burrs, which may be introduced into the bore 16 during manufacture. At the same time, the diameter is limited to cause frictional engagement so that the medicament is less likely to be inadvertently dislodged from the bore prior to activation of the device. An oil can be added to the bore to increase the tendency of the medicament to remain in the bore; an oil will also assist in penetration through the skin.

The diameter of the medicament is not at all arbitrary; it has been found that the introduction of a pin with a diameter of about 2 mm or less is substantially painless. Such is not the case for larger diameters, and larger diameter medicaments may generally only be administered via a trocar.

The active ingredient can be a peptide or a protein. Examples of such peptides include growth hormone releasing peptide (GHRP), luteinizing hormone-releasing hormone (LHRH), somatostatin, bombesin, gastrin releasing peptide (GRP), calcitonin, bradykinin, galanin, melanocyte stimulating hormone (MSH), growth hormone releasing factor (GRF), amylin, tachykinins, secretin,

- 9 -

parathyroid hormone (PTH), enkephalin, endothelin, calcitonin gene releasing peptide (CGRP), neuromedins, parathyroid hormone related protein (PTHrP), glucagon, neurotensin, adrenocorticotrophic hormone (ACTH), peptide
5 YY (PYY), glucagon releasing peptide (GLP), factor VIII, vasoactive intestinal peptide (VIP), pituitary adenylated cyclase activating peptide (PACAP), motilin, substance P, neuropeptide Y (NPY), TSH, and analogs and fragments thereof. Other active ingredients include insulin,
10 adrenaline, xylocaine, morphine, a glucocorticoid (e.g., dexamethasone), atropine, a cytostatic compound, estrogen, androgen, interleukins, digitoxin, biotin, testosterone, heparin, cyclosporin, penicillin, vitamins, antiplatelet activating factor agents (e.g.,
15 ginkgolides), or diazepam.

In order to provide instant delivery of the active ingredient, the carrier should be water soluble. Examples of water soluble carriers include hyaluronic acid, cellulose, e.g., hydroxypropylmethyl cellulose
20 (HPMC), carboxymethyl cellulose (CMC), and hydroxyethyl cellulose (HEC), polyalcohols, e.g., mannitol, sugars, e.g., dextrose, mannose, and glucose, gelatin, polyvinylpyrrolidone, and starches. The carrier can also be water insoluble, but biodegradable to provide
25 sustained delivery. Examples of suitable carriers include water insoluble polyesters of L-lactic acid, D-lactic acid, DL-lactic acid, L-lactide, D-lactide, DL-lactide, glycolide, glycolic acid, capralactone, and any optically active isomers, racemates, or copolymers
30 thereof.

The following are illustrative examples of the parenteral administration of drugs in solid form as compared to the conventional liquid form, and are intended to show that the two means of administration
35 have similar pharmaceutical efficacy.

- 10 -

EXAMPLE 1

A test was conducted with Insulin Human Recombinant (IHR) and Insulin Bovine Pancreas (IBP). IHR is pure water soluble insulin; IBP is zinc insulin, water insoluble and prepared usually using 16% glycerol. IHR and IBP represent about 26 Insulin Units (IU) per mg.

Different doses of insulin were compared with a conventional injectable formulation. In an in vivo test of hypoglycemic effect on rats, all these formulations were found as effective in terms of intensity and rapidity of action.

Insulin can be delivered as a dry solid and acts exactly like the usual parenteral formulation for bolus injection. The quantities needed with the device of the present invention are small enough to be administered in solid form as a 2 mm long cylinder with a 0.45 mm diameter. Patients can readily perform virtually painless introduction of solid insulin with the device of the present invention. This form of insulin is also stable for a longer time at room temperature and less expensive than the usual liquid form.

EXAMPLE 2

A formulation of a somatostatin analogue, D-Nal-cyclo [Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH₂ was made into injectable tablets by associating the dry material with gelatin and polyvinylpyrrolidone (PVP, 5-10%). The tablets were injected and compared to conventional solutions in terms of pharmacokinetic profiles. The methods gave substantially the same pharmacological results.

EXAMPLE 3

A synthetic anti-PAF, 4,7,8,10-tetrahydro-1-methyl-6-(2-chlorophenyl)-9-(4-methoxyphenyl-thiocarbamoyl)-pyrido-[4',3'-4,5] thieno [3,2-f]-1,2,4-triazolo [4,5-a] 1,4-diazepine, and a natural anti-PAF,

- 11 -

ginkgolide B, were compared to conventional administration. The synthetic anti-PAF cannot conventionally be used parenterally because of its insolubility. Nevertheless, a very good correlation
5 between pharmacological effect and blood concentration has been observed. Ginkgolide B is slightly soluble. For the same dose of product in solution form (pH 8.75), the effect was the same after initial injection but lasted only 2 hours with the solution whereas the effect
10 lasted 24 hours with the solid dry formulation.

EXAMPLE 4

A prolonged formulation of decapeptyl (1 month) was made by a molding process with a molding machine into a shape of 0.8 mm diameter and some cm long.
15 Polylactidecoglycolide (PLGA, 80%) was used. The pharmacokinetically controlled delivery was equivalent to that of an implant or microspheres and the solid form was perfectly injectable subcutaneously or intravenously when the device was used in different species (rabbit, dog,
20 rat, and pig).

Other Embodiments

It will be understood that the claims are intended to cover all changes and modifications of the preferred embodiments of the invention herein chosen for the
25 purpose of illustration which do not constitute a departure from the spirit and scope of the invention.

What is claimed is:

- 12 -

1. A needle-less device capable of parenteral administration of a medicament, said device comprising a barrel member and a plunger, said barrel member having first and second ends and a bore for receipt of said medicament in solid form, said bore extending from said first end to said second end of said barrel, said plunger comprising an elongated rod of substantially the same outside diameter as the inside diameter of said bore, said rod being inserted into the bore at said second end of said barrel, said plunger being capable of movement in said bore to push said medicament out said first end of the barrel member, through the skin of a patient when said barrel member is pressed against the skin of the patient and when the medicament is of sufficient structural strength to penetrate the skin of the patient.

2. The device of claim 1 further comprising a sleeve, said sleeve being affixed to said plunger and said sleeve being in sliding engagement with the exterior surface of said barrel member, said sleeve having first and second ends.

3. The device of claim 2 wherein said barrel includes two spaced protruding ring members, and wherein said first end of said sleeve has an inwardly extending shoulder, said inwardly extending shoulder retaining said one end of said sleeve in sliding movement on said barrel member between said two ring members on said barrel.

4. The device of claim 2 wherein the plunger comprises a rod affixed to an end cap, said second end of said sleeve being affixed to said end cap.

- 13 -

5. The device of claim 4 wherein said second end of sleeve is affixed to the end cap by frictional engagement.

6. The device of claim 2 further comprising a
5 second shoulder extending inwardly from said sleeve, said second shoulder being spaced from the first shoulder, said second shoulder in combination with one of said protruding ring members on the barrel member limiting the travel of the plunger rod in said bore of the barrel
10 member.

7. The device of claim 6 wherein the limit of travel of said rod is such that no more than about 2 mm of the rod extends beyond said first end of the barrel member.

15 8. The device of claim 6 wherein the limit of travel of said rod is such that none of the rod of the plunger member extends beyond said first end of the barrel member.

9. The device of claim 1 wherein said first end
20 of the barrel member has a nose cone shape.

10. The device of claim 1 further comprising a medicament in the bore of the barrel member.

11. The device of claim 10 wherein the medicament has the shape of one end of a toothpick and includes a
25 point with a taper back to a cylindrical portion and wherein said point in said bore is aligned towards said first end of the barrel member.

- 14 -

12. The device of claim 11 wherein the medicament has a diameter in the cylindrical portion of from about 0.2 to about 2 mm and the overall length of the medicament is from about 1 mm to about 5 cm.

5 13. The device of claim 10 further comprising a seal of a biologically compatible material covering the end of said bore located at said first end of said barrel member.

10 14. The device of claim 13 wherein the biologically compatible material is selected from the group consisting of cellulose and gelatin.

15 15. A medicament adapted to be administered parenterally to a patient, said medicament having a diameter of from about 0.2 to about 2 mm and a length of from about 1 mm to about 5 cm, and said medicament having sufficient structural integrity to penetrate the skin of the patient.

20 16. The medicament of claim 15 wherein said medicament comprises substantially 100% active ingredient.

17. The medicament of claim 15 wherein the diameter of said medicament is from about 0.2 to about 0.8 mm.

25 18. The medicament of claim 15 wherein the diameter of said medicament is from about 0.25 to about 0.50 mm.

- 15 -

19. The medicament of claim 15 wherein the medicament has a crush strength of at least about 8 killipoise in the longitudinal direction.

20. The medicament of claim 15 wherein said
5 medicament has the shape of a toothpick with a frustoconical point at one end thereof.

21. A medicament adapted to be administered parenterally, said medicament comprising at least about 10% active ingredient, said medicament having a diameter
10 of from about 0.2 to about 2 mm and a length of from about 1 mm to about 5 cm, and said medicament having a crush strength of at least about 8 killipoise in the longitudinal direction.

22. The medicament of claim 21 wherein the
15 diameter of said medicament is from about 0.2 to about 0.8 mm.

23. A method of administering a medicament parenterally to a patient without the use of a needle, said method comprising bringing a medicament having a
20 sufficient structural strength to penetrate the patient's skin into contact with the patient's skin and forcing the medicament through the skin.

24. A needle-less device capable of parenteral administration of a medicament, said device comprising a
25 barrel member and a gas supply mechanism, said barrel member having first and second ends and a bore for receipt of said medicament in solid form, said bore extending from said first end to said second end of said barrel, said gas supply mechanism comprising a reservoir,
30 a gas supply valve and an operating button, said

- 16 -

operating button being depressible to allow gas to flow from said reservoir through said valve and into said barrel member, said gas being capable of moving said medicament in said bore to push said medicament out said
5 first end of the barrel member and through the skin of a patient when said barrel member is pressed against the skin of the patient and said button is depressed and when the medicament is of sufficient structural strength to penetrate the skin of the patient.

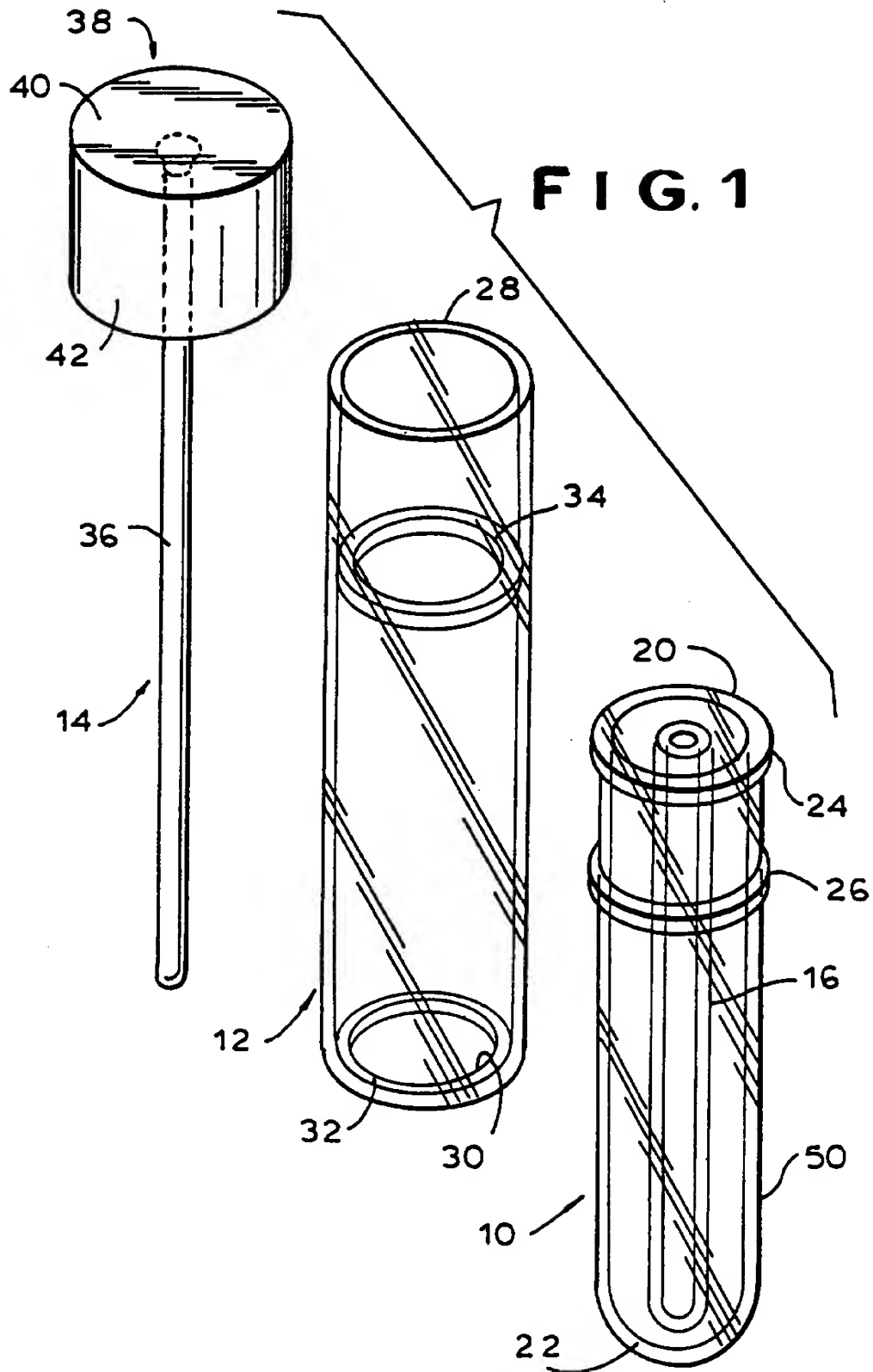
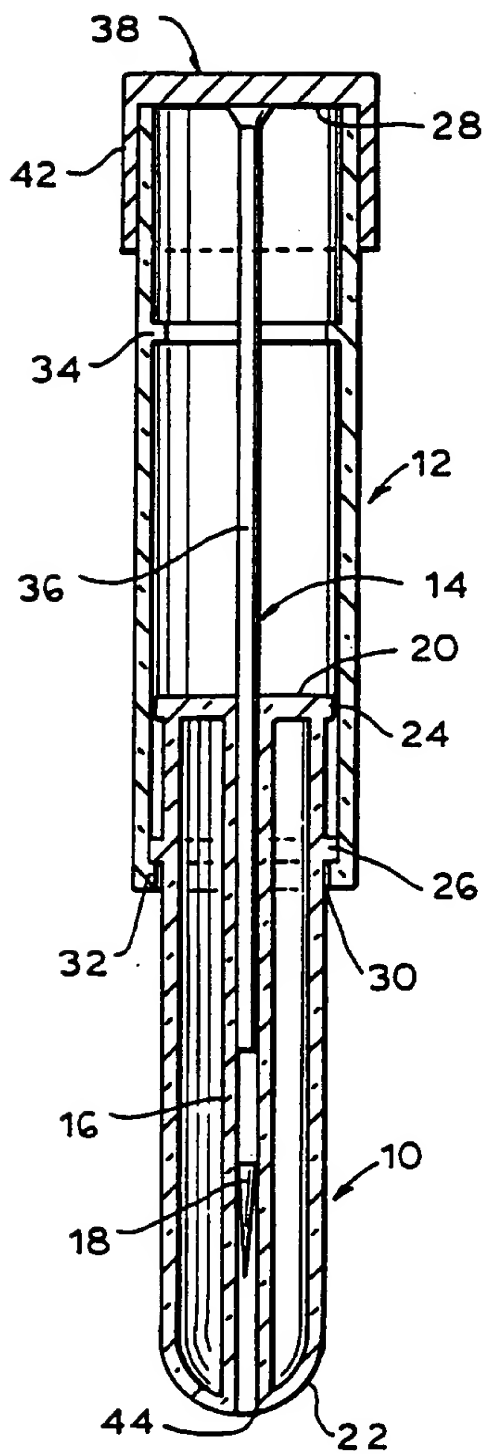
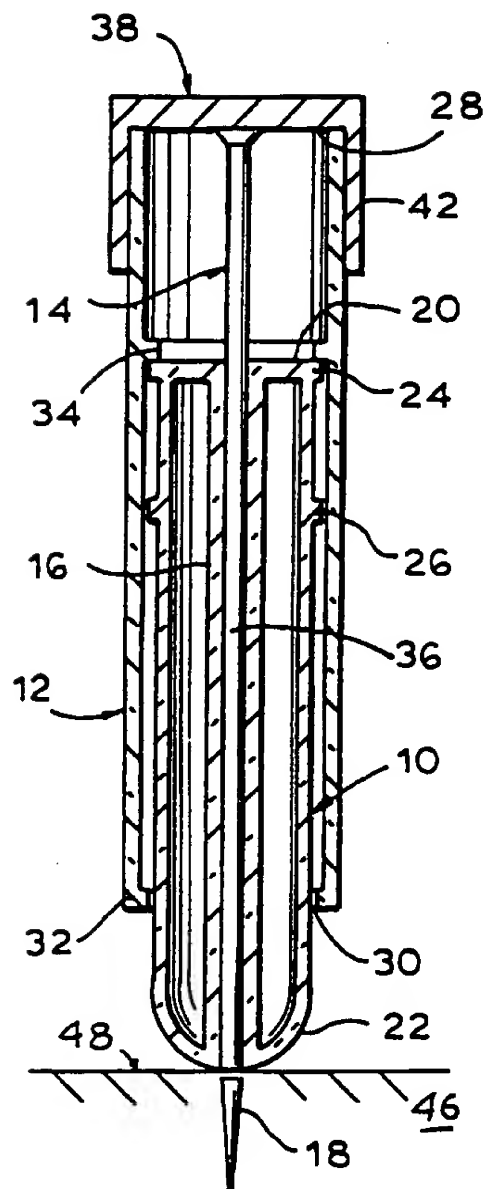
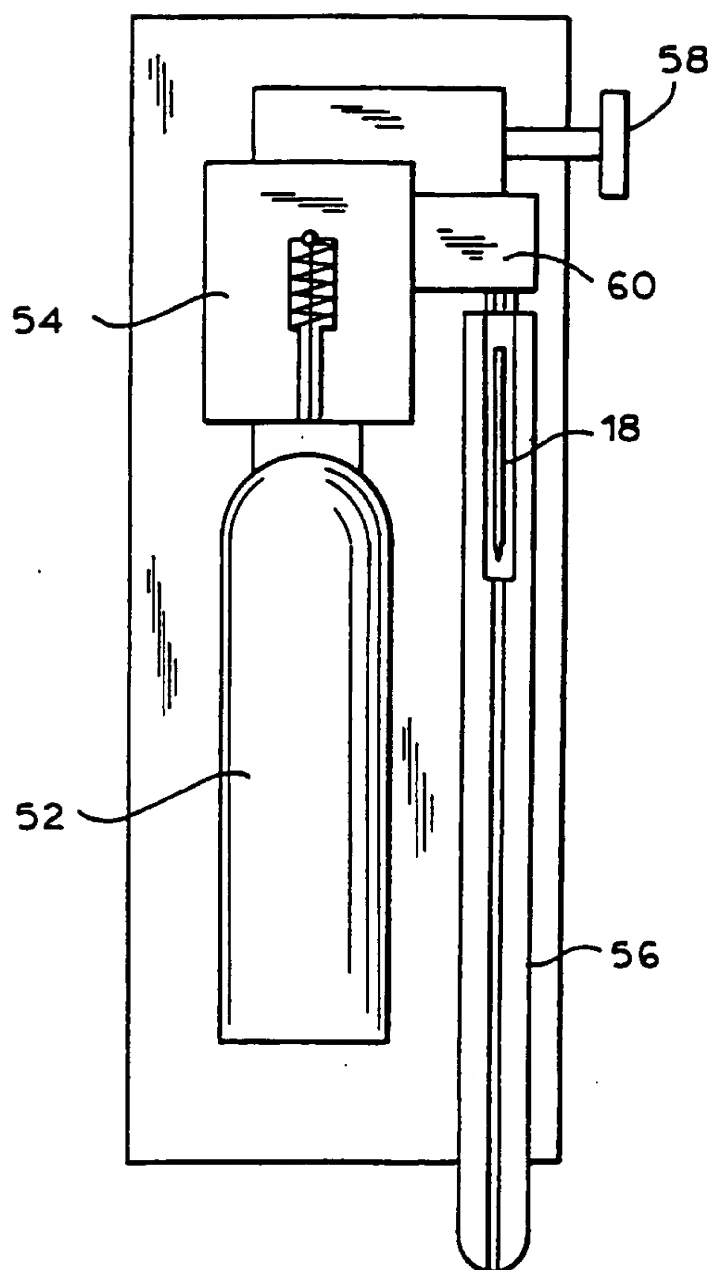


FIG. 2**FIG. 3**

**FIG. 4**

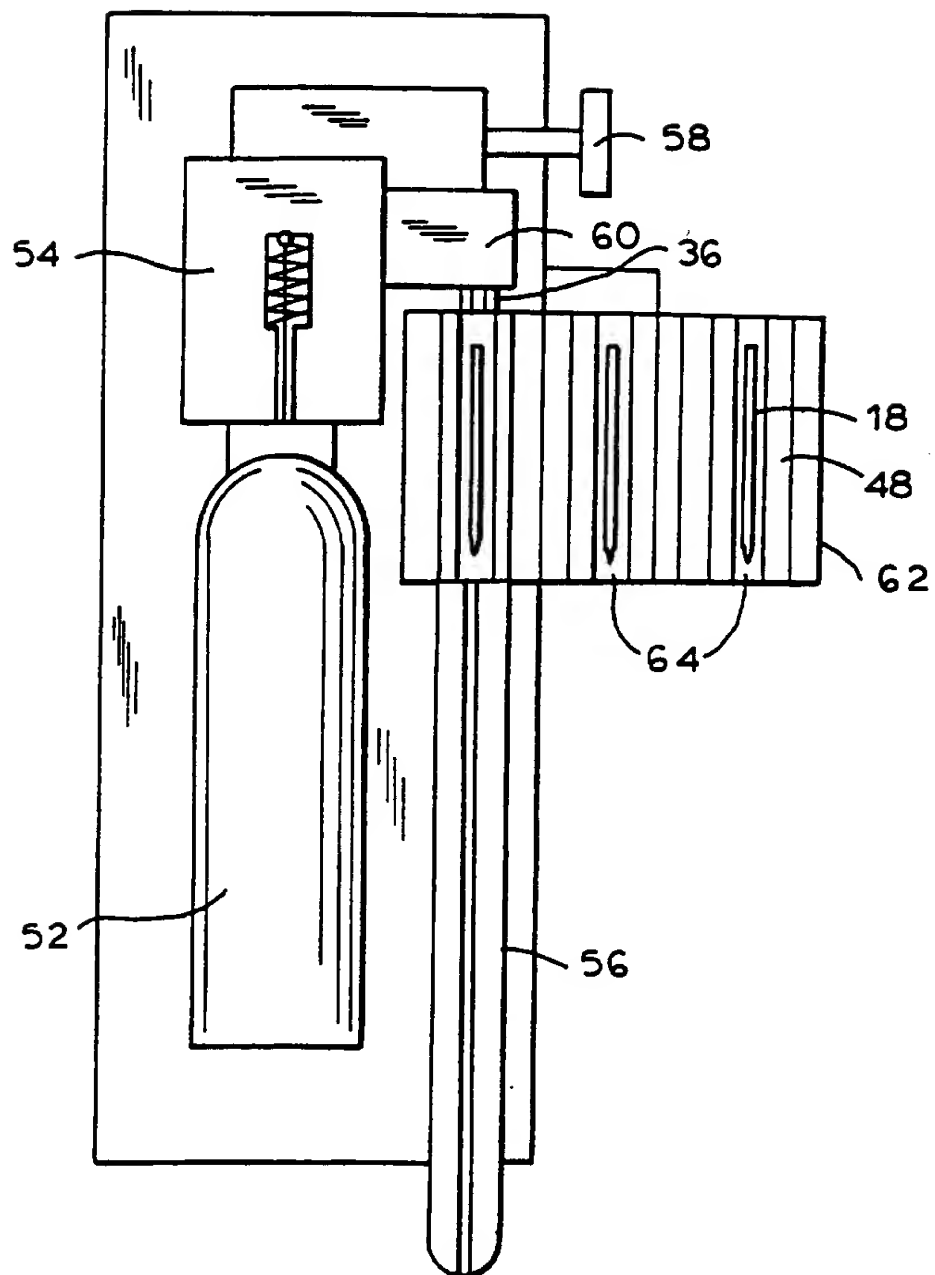


FIG. 5

INTERNATIONAL SEARCH REPORT

national Application No
PCT/IB 95/00841

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M37/04 A61M5/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 091 554 (MITSUITOATSU CHEMICALS INC) 4 August 1982	1,10-12, 15-22
Y	see page 2, line 15 - line 30 ---	2-9
Y	NL,A,8 901 124 (N.V NEDERLANDSCHE APPARATENFABRIEK) 3 December 1990 see figures ---	2-9
X	EP,A,0 049 068 (MINNESOTA MINING AND MANUFACTURING CO) 7 April 1982 see abstract; figures ---	15-22,24
X	US,A,4 697 575 (HOROWITZ) 6 October 1987 see claims 1,6; figures ---	15-22
X	WO,A,93 23110 (VAN DE WIJDEVEN) 25 November 1993 see abstract; figures ---	24
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

Date of the actual completion of the international search

12 February 1996

Date of mailing of the international search report

16.02.1996

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Kousouretas, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 95/00841

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US,A,4 820 267 (HARMAN) 11 April 1989 see figures</p> <p>-----</p>	1-9

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 95/00841

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-2091554	04-08-82	JP-A- 57116008 JP-A- 58065211 CH-A- 650405 DE-A- 3200763 FR-A,B 2497661	19-07-82 18-04-83 31-07-85 25-11-82 16-07-82
NL-A-8901124	03-12-90	NONE	
EP-A-49068	07-04-82	US-A- 4326524 AR-A- 229104 AU-B- 539016 AU-B- 7573981 CA-A- 1138333	27-04-82 15-06-83 06-09-84 08-04-82 28-12-82
US-A-4697575	06-10-87	US-A- 4815449	28-03-89
WO-A-9323110	25-11-93	NL-A- 9200844 AU-B- 4358993 CA-A- 2134770 EP-A- 0686053 JP-T- 7509622	01-12-93 13-12-93 25-11-93 13-12-95 26-10-95
US-A-4820267	11-04-89	NONE	